




Ketamine-induced urological toxicity: potential mechanisms and translation for adults with mood disorders receiving ketamine treatment

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Abstract

Intravenous (IV) ketamine has been shown to have rapid and robust antidepressant effects in adults with treatment-resistant depression (TRD). Urological toxicity has been observed in chronic ketamine abusers as evidenced by dysuria, urgency, and hematuria. The foregoing observation provides the basis for evaluating whether ketamine-induced urological toxicity (KIUT) is associated with sub-anesthetic doses of ketamine (0.5–1.0 mg/kg) in adults with mood disorders. The overarching objective of this article is to identify potential mechanisms of KIUT which appears to be dose and frequency dependent. Available research indicates that high-frequency ketamine is associated with disruption of the urothelial barrier as well as direct ketamine toxicity (i.e., decreased expression of junction proteins) in KIUT of the bladder. Chronic and high-frequency ketamine use is also associated with bladder inflammation mediated via neurogenic and IgE inflammation. Other non-mutually exclusive causes are nerve hyperplasia, hypersensitivity, cell apoptosis, microvascular damage, and overexpression of carcinogenic genes. Notwithstanding the evidence of KIUT in ketamine abusers, there is no evidence that ketamine and/or esketamine treatment in adults with mood disorders is associated with KIUT. However, all patients receiving ketamine/esketamine for mood disorder treatment should be queried about genitourinary symptoms during acute and, where applicable, maintenance dosing.

Keywords Major depressive disorder · Depression · Bipolar disorder · Ketamine · CRTCE · Esketamine

Introduction

Ketamine is a dissociative anesthetic that has been used globally for over 50 years (Morgan et al. 2012). Over the past two decades, intravenous (IV) ketamine has been shown to have rapid and robust antidepressant effects in patients with treatment-resistant depression (TRD) at sub-

anesthetic doses (0.5–1.0 mg/kg infused over 40 min) (McIntyre et al. 2020). TRD is defined by the lack of response to two or more trials of antidepressant drugs, and it impairs productivity, social functioning, and overall health of depressed individuals (Rush et al. 2006; Walker et al. 2015). More recently, intranasal (IN) esketamine, the S-enantiomer of ketamine, was approved for unipolar TRD

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and has also demonstrated short-term antidepressant effects (28–84 mg administered 2 times/week for < 6 months) (Daly et al. 2018; Kim et al. 2019). Antidepressant effects may be observed after a single ketamine infusion (0.5–1.0 mg/kg); however, effects are lost after 1–2 weeks, requiring repeated infusions (0.5–1.0 mg/kg every 1–4 weeks) to maintain antidepressant effects (Kryst et al. 2020). For IN esketamine, the response appears to sustain for more than 2 months even with a lower dosing frequency (1 time/week or every 2 weeks) (Daly et al. 2018). While the safety and tolerability of short-term doses have been well characterized, the safety profile of long-term IV ketamine and IN esketamine treatment (≥ 6 months) at antidepressant doses (ketamine: 0.5–1.0 mg/kg every 1–4 weeks; esketamine: 28–84 mg administered 2 times/week) has yet to be established (Na and Kim 2021; Rodrigues et al. 2020; Short et al. 2018).

Recommendations for prescribing ketamine/esketamine in adults with mood disorders in both acute and maintenance phases provide the impetus for a better understanding of specific safety concerns. Ketamine-induced urological toxicity (KIUT) has been associated with chronic and frequent high-dose exposure in ketamine abusers (dose: ≥ 0.125 g/session; frequency: ≥ 1 day/month) (Winstock et al. 2012). Ketamine-induced urological toxicity secondary to ketamine abuse was first described in 2007. The evidence appeared that chronic ketamine abusers experienced KIUT as evidenced by urinary frequency, urgency, hematuria, and dysuria (Shahani et al. 2007). Chronic ketamine abuse is also reported to affect the upper urinary tract, where hydronephrosis is observed, and is associated with vesicoureteral reflux and ureteral stenosis (Chu et al. 2008; Lai et al. 2012). Winstock et al. (2012) have reported 26.6% of ketamine abusers ($n = 1285$) experienced urological symptoms. The risk of urological complications is directly related to ketamine dose and frequency, where higher doses (≥ 0.25 g/session) and frequency of use (≥ 5 days/month) are associated with higher rates of lower abdominal pain, hematuria, and burning sensation during urination (Winstock et al. 2012). Complicating the interpretation of KIUT in individuals who are abusing ketamine is a possibility that other substances of abuse are often co-abused which may further contribute to KIUT in this population. Disparate mechanisms likely are contributing to KIUT in polysubstance abusers; below, we reviewed mechanisms implicated for KIUT specifically related to ketamine.

While urological side effects have been observed in chronic ketamine abusers, the relative risk of urological complications of IV ketamine (0.5–1.0 mg/kg every 1–4 weeks) and IN esketamine (28–84 mg administered 2 times/week) at long-term (≥ 6 months) antidepressant doses appears to be minimal. Survey data of IV ketamine providers suggests that urological

complications are rare with short-term depression maintenance treatment (prevalence = 0.1%, duration: < 6 months). There is also no evidence suggesting that short-term ketamine treatment in mood disorders is associated with urological toxicity. Similarly, two clinical studies have reported a low occurrence (< 10%) of urological complications in patients with TRD when examining the safety and efficacy of short-term IN esketamine treatment (Daly et al. 2019; Wajs et al. 2020). Albeit the low prevalence of urological toxicity in short-term clinical trials, it is still unknown whether such safety profiles could be maintained in long-term studies or clinical interventions. Currently, there are limited studies that investigate the long-term safety (≥ 6 months) of IV ketamine and IN esketamine treatments (Feifel et al. 2020; Findeis et al. 2020; Short et al. 2018).

Therefore, it would be useful to point out the potential urological complications in long-term depression maintenance treatment and identify possible mechanisms of KIUT in chronic ketamine abusers. This would inform health care practitioners of the possibility of urological complications in long-term studies and interventions, and allow them to take appropriate measures when such symptoms arise. Of note, the current review focused on the mechanisms of ketamine, rather than esketamine. However, due to the similarity between the two substances, mechanisms and risk are likely to have significant overlap with ongoing research in this area (Findeis et al. 2020).

Pharmacology of ketamine

Ketamine is a lipophilic molecule that is rapidly absorbed in the human body through oral, nasal, and parenteral routes (Castellani et al. 2020; Peltoniemi et al. 2016; Zanos et al. 2018). Upon absorption, ketamine crosses the blood-brain barrier (BBB) and binds to the phencyclidine site of NMDARs in neurons, thus blocking the transmembrane ion flux and acting as a non-competitive antagonist (Malinovsky et al. 1996; Zanos et al. 2018). The anesthetic effect of ketamine is widespread in the central nervous system (CNS) as NMDARs are present in many tissues, such as the cerebral cortex, cerebellum, brainstem, and spinal cord, that are important in neuronal signal transduction (Myers et al. 2016).

The primary site of ketamine biotransformation is in the liver, where it is metabolized by cytochrome P450 enzymes to norketamine through the N-demethylation pathway (Chen and Chen 2010). Norketamine is then excreted in bile and expelled in the urine (Peltoniemi et al. 2016). As a result of the first-pass liver metabolism, oral administration of ketamine has a poor bioavailability (17%), whereas bioavailability via the parenteral route is close to 100% (Grant et al. 1981; Malinovsky et al. 1996). For intranasal administration, the bioavailability is approximately 50% (Peltoniemi et al. 2016).

Clinical findings of ketamine-induced urological toxicity

The clinical symptoms of KIUT vary greatly with respect to disease progression (Jhang et al. 2015). Common symptoms of KIUT are dysuria, hematuria, urinary urgency, urinary frequency, and post-micturition dribble (Shahani et al. 2007). Ultrasound studies have reported reduced bladder capacity with thickened bladder wall, bilateral hydronephrosis, and hydroureter following chronic abuse of ketamine (Pappachan et al. 2014; Lee et al. 2009). Cystoscopic findings from chronic ketamine abusers with KIUT ($n = 16$) have detailed fragile bladder mucosa, mucosal laceration after bladder distention, and glomerular hemorrhage (CL Lee et al. 2013). Hematoxylin-eosin stains of KIUT bladder have also revealed denuded urothelium, alongside mild inflammation in the mucosa with eosinophils, lymphocytes, and plasma cells infiltration (Wei et al. 2013). Ketamine-induced urological toxicity has been associated with chronic and frequent high-dose exposure in ketamine abusers (dose: ≥ 0.125 g/session; frequency: ≥ 1 days/month) (Winstock et al. 2012). The severity of symptoms was observed to be dose and frequency dependent, where higher doses (≥ 0.25 g/session) and frequency of use (≥ 5 days/month) were associated with increased rates of urinary frequency, hematuria, and burning sensation in urination (Winstock et al. 2012). Although there is no observed sex difference in KIUT symptom prevalence, female ketamine abusers tend to have more serious urinary symptoms than males (9.7% vs 3.8%, $n = 1614$) (Chen et al. 2014).

Potential mechanisms of KIUT

The extant literature suggests multiple non-mutually exclusive possible mechanisms of KIUT in chronic ketamine abusers, including urothelial barrier disruption, bladder inflammation, ketamine direct toxicity, nerve hyperplasia and hypersensitivity, cell apoptosis, microvascular damage, and overexpression of carcinogenic genes (Table 1).

Urothelial barrier disruption

Damage of the urothelial barrier has been postulated as a possible mechanism of KIUT. A decreased expression of intercellular junction proteins (E-cadherins and zonula occludens-1) has been reported in bladder tissues of chronic ketamine abusers and rats with KIUT, which suggests a disruption in cell-cell junction stability, thereby disrupting the urothelial barrier (Duan et al. 2017; Wang et al. 2017). Intercellular junction proteins are crucial in cell adhesions and the maintenance of epithelial barrier function by preventing substances from entering the bladder wall (Castellani et al. 2020). Thus, chronic exposure to ketamine in the bladder may lead to

urothelial barrier damage by reducing the expression of junction proteins, which allows urinary irritants to enter the compromised bladder wall and provoke inflammatory responses (Fig. 1) (Jhang et al. 2015). Exploring the relationship between chronic ketamine abuse and reduced expression of junction proteins in the urothelial barrier will be useful in elucidating pathophysiological mechanisms in KIUT.

The downregulation of junction proteins could also lead to epithelial-to-mesenchymal transition (EMT), a process where the urothelium loses apical-basal polarity and cell-cell adhesion, experiences phenotypical changes, and develops invasive properties (Lamouille et al. 2014; Thiery et al. 2009). It has been shown that the loss of E-cadherin is paralleled by the acquisition of mesenchymal markers such as vimentin and fibronectin, indicating the development of EMT in KIUT of the bladder (Wang et al. 2017). The exposure of mesenchymal cells to the surroundings may promote their activation and further result in fibrosis, a condition defined by the excessive accumulation of extracellular matrix (ECM) components like collagen and fibronectin (Wynn and Ramalingam 2012). Additionally, studies have revealed that transforming growth factor- $\beta 1$ (TGF- $\beta 1$) signaling activates several transcription factors (Snail, Slug, and Twist) and induces EMT, which may contribute to fibrosis in KIUT of the bladder (Lamouille et al. 2014; Thiery et al. 2009). Hence, more studies are needed to elucidate the implication of downregulated junction proteins and how these factors can initiate EMT progression in KIUT via the TGF- $\beta 1$ pathway.

Bladder inflammation

Ketamine-induced urological toxicity of the bladder commonly displays a denuded epithelium, infiltration of macrophages, neutrophils, eosinophils, mast cells in the mucosa, increased collagen deposition, and elevated serum interleukin (IL) 1, 5, 6, and 17, which demonstrate the activation of inflammatory processes in bladder tissue (Castellani et al. 2020). Inflammation is further confirmed by the presence of inflammatory markers including, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS), and matrix metalloproteinase-9 (MMP-9), identified through immunohistochemical staining (Gu et al. 2014; Lin et al. 2015). Among the 3 markers, iNOS is particularly important since it is associated with many inflammatory mediators, such as cytokines, prostaglandin E2, and the COX pathway, leading to robust downstream inflammatory responses and possibly interstitial fibrosis in the bladder (Jhang et al. 2015).

Furthermore, the transcription factor NF- κ B is found to be responsible in this process by regulating downstream COX-2 gene expression (Juan et al. 2015). It has been postulated that the stimulation of ketamine on bladder cells leads to the disinhibition of NF- κ B by BAY 11-7082 (Fig. 2). Subsequently, nuclear translocation of NF- κ B occurs at the promoter region

Table 1 Potential mechanisms of ketamine-induced urological toxicity

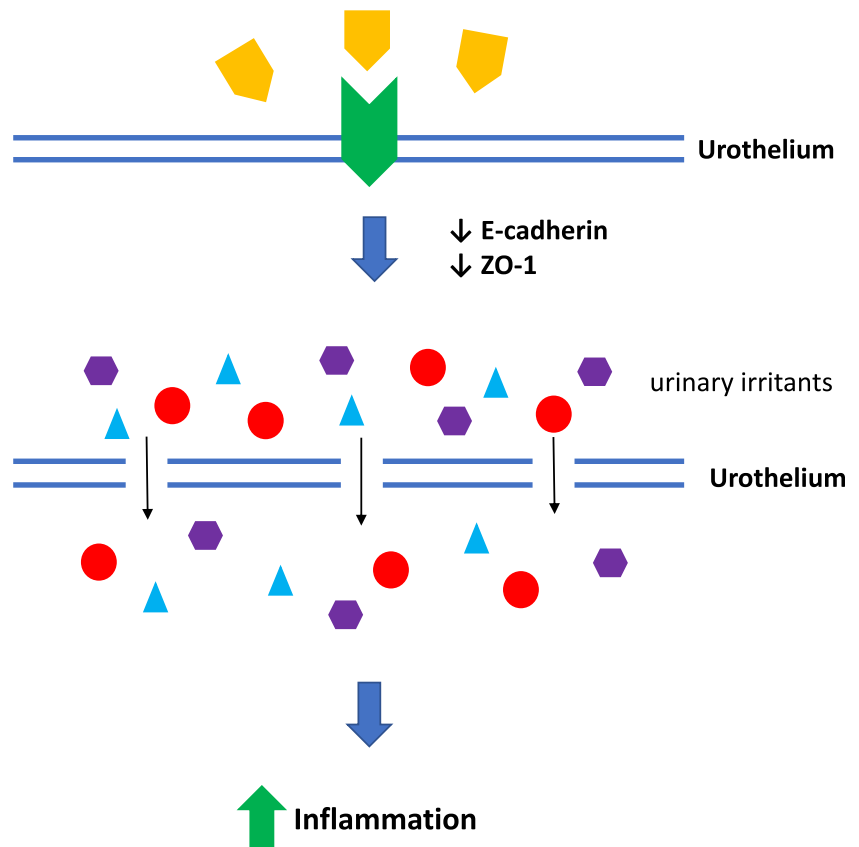
Proposed mechanisms	Summary
1. Urothelial barrier disruption	<p>Ketamine may damage the urothelial barrier by reducing the expression of junction proteins (E-cadherins and zonula occludens-1), which allows urinary irritants to enter the compromised bladder wall and provoke inflammatory responses.</p> <p>TGF-β1 signaling activates several transcription factors (Snail, Slug, and Twist) and induces EMT, which may contribute to fibrosis in KIUT of the bladder.</p>
2. Bladder inflammation	<p>iNOS is associated with many inflammatory mediators, such as cytokines, prostaglandin E2, and the COX pathway, leading to downstream inflammatory responses and possibly interstitial fibrosis in the bladder.</p> <p>Stimulation of ketamine on bladder cells may lead to the disinhibition of NF-κB by BAY 11-7082. Nuclear translocation of NF-κB then occurs where it binds to the promoter region of the COX-2 gene and upregulates its gene expression. This results in the secretion of prostaglandin and inflammation in the bladder.</p>
3. Ketamine-mediated toxicity	<p>After the biotransformation process in the liver, ketamine and its metabolites can last in the urine for 14 days and be exposed to bladder tissue continuously. Ketamine in the urine may trigger direct damage and inflammation in the bladder.</p> <p>Ketamine may also induce toxicity in the bladder by provoking a large release of calcium (Ca^{2+}) ions from the endoplasmic reticulum (ER) into the cytosol. The sustained increase in intracellular Ca^{2+} level could cause stress in the mitochondria and the ER, which results in cell apoptosis. Furthermore, hydroquinone, a ketamine metabolite, directly fragments DNA and chromosomes in mouse bladder cells.</p>
4. Nerve hyperplasia and hypersensitivity	<p>An antigen-IgE antibody complex may form upon entry of ketamine metabolites into the bladder, which recruits eosinophils and further enhances the inflammatory response.</p> <p>Elevated IgE levels, upregulation of neurotrophins, and nerve hyperplasia in bladder tissue could result in hypersensitivity and intense pain.</p>
5. Cell apoptosis	<p>Increased apoptotic cells and overexpression of BAX were observed in KIUT of the bladder. Apoptotic cells in the bladder may undergo secondary necrosis, a process where cell membranes are permeable to macromolecules and eventually leads to inflammatory responses.</p>
6. Microvascular damage	<p>Antagonism of NMDARs by ketamine may result in vessel impairment and chronic inflammation. Microvascular injury in the bladder may cause local ischemia as well, which could lead to dysuria and pelvic pain.</p>
7. Overexpression of carcinogenic genes	<p>Urothelial atypia, moderate to high immunoreactivity of p53 and Ki-67, was observed in KIUT of the bladder, which resembles carcinoma in situ.</p> <p>High expression of phosphorylated transgelin was found in bladder tissue of animals with KIUT. Phosphorylation of transgelin may inactivate its actin-binding and tumor-suppressing function, which could lead to the development of cancer in the organ. The low expression of E-cadherin is also correlated with cancer progression.</p>

of the COX-2 gene and upregulates its gene expression. The upregulation of COX-2 then results in the secretion of prostaglandin, leading to inflammation of the bladder (Juan et al. 2015). It should be noted that available evidence regarding this pathway is mixed with some studies suggesting that COX-2 acts upstream of NF- κ B, where it activates the transcription factor (Chen et al. 2013). Therefore, future research will be required to elucidate the role of enzymes involved in the inflammatory response to ketamine.

Ketamine-mediated toxicity

Direct toxic effects of ketamine in urine have been considered as a plausible mechanism for the bladder damage present in KIUT (Shahani et al. 2007). After the biotransformation process in the liver, ketamine and its metabolites can last in the urine for 14 days and be exposed to bladder tissue continuously (Parkin et al. 2008). Studies have proposed ketamine in urine might trigger direct damage and inflammation in the

Fig. 1 Disruption of the urothelial barrier by ketamine and its metabolites. Ketamine could damage the urothelial barrier by reducing the expression of junction proteins (E-cadherins and zonula occludens-1). Downregulation of these proteins would allow the entry of urinary irritants to the bladder wall and induce inflammation



bladder (Chuang et al. 2013). The presence of denuded urothelium, ulceration, and fibrosis could explain the direct bladder injury by ketamine, which is similar to cystitis caused by cytotoxic agents like cyclophosphamide (CP) and mitomycin-C (Payne et al. 2013).

Baker et al. (2016) has demonstrated ketamine can also induce toxicity in the bladder by provoking a large release of

calcium (Ca^{2+}) ions from the endoplasmic reticulum (ER) into the cytosol. This damage is dose and time dependent. The sustained increase in intracellular Ca^{2+} level can cause stress in the mitochondria and the ER, which results in cell apoptosis (Fig. 3). Furthermore, it has been found that hydroquinone, a ketamine metabolite, directly fragments DNA and chromosomes in mouse bladder cells (Enguita and Leitão 2013; Tan

Fig. 2 Upregulation of COX-2 gene expression through NF- κ B signaling pathway. Ketamine stimulation of bladder cells leads to disinhibition of NF- κ B by BAY 11-7082. Nuclear translocation of NF- κ B occurs subsequently where it binds to the promoter region of the COX-2 gene and upregulates its gene expression. The upregulation of the COX-2 gene then results in the secretion of prostaglandin, leading to inflammation of the bladder

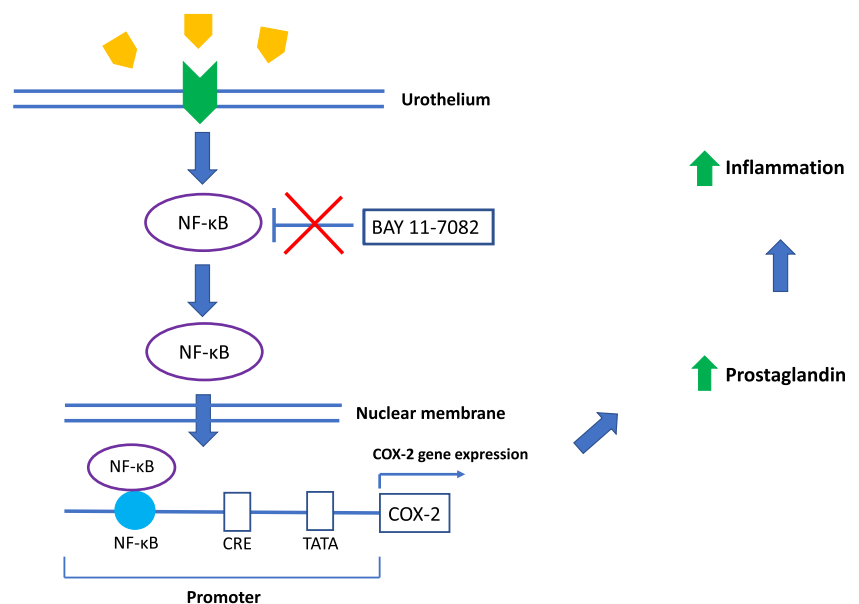
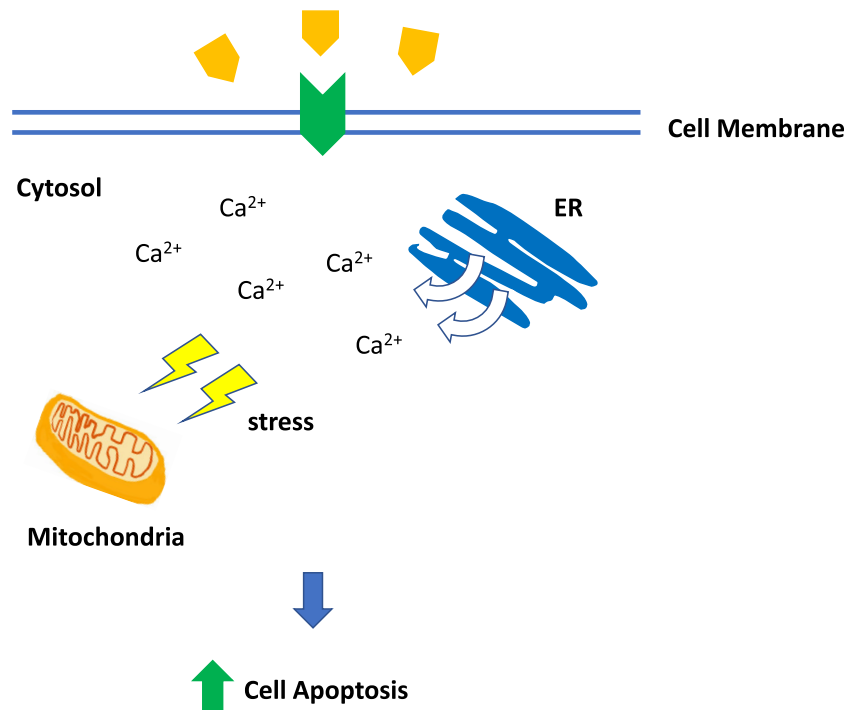


Fig. 3 Endoplasmic reticulum and mitochondrial stress induced by elevated intracellular Ca^{2+} levels. Ketamine may exert toxicity to the bladder by provoking the release of Ca^{2+} from the ER into the cytosol. The increase in intracellular Ca^{2+} would cause stress to the mitochondria and ER, which results in cell apoptosis



et al. 2011; Wai et al. 2013). As a result, hydroquinone may play an important role in the pathogenesis of KIUT. Further investigations on the concentration of hydroquinone in urine are required to indicate its role in KIUT in humans.

Nerve hyperplasia and hypersensitivity

The immune system is believed to be involved in the pathogenesis of KIUT. Apart from eosinophil infiltration, the IgE level is also found to be higher in blood and bladder tissue of chronic ketamine abusers with KIUT (Jhang et al. 2016). It has been speculated that an antigen-IgE antibody complex is formed upon entry of ketamine metabolites into the bladder, which recruits eosinophils and further enhances the inflammatory response (Teegavarapu et al. 2005). Moreover, a separate study has suggested elevated IgE levels are strongly associated with hypersensitivity, where chronic ketamine abusers with KIUT experience more intense bladder pain (Jhang et al. 2014).

In addition, nerve hyperplasia has been noticed in the bladder tissue of chronic ketamine abusers with KIUT and could be the cause of hypersensitivity (Jhang et al. 2019). Significant nerve bundles and stromal neurogenesis are observed in the deep lamina propria of the urothelium (Baker et al. 2013; Jhang et al. 2018). The expression levels of neurotrophins, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), growth-associated protein 43 (GAP-43), tropomyosin receptor kinase A (Trk A), and their receptors are upregulated in the bladder mucosa of chronic ketamine abusers with KIUT (Jhang et al. 2019). Neurotrophins in the bladder are responsible for regulating sensory afferents and modulating the growth of

neurons; hence, their upregulation could result in nerve hyperplasia and ultimately hypersensitivity (Cruz 2014; Jhang et al. 2019). The increased levels of neurotrophins are also shown to be correlated with bladder pain in chronic ketamine abusers with KIUT (Jhang et al. 2019). Nonetheless, some studies have shown opposite results where the expression levels of neurotrophins are lower in chronic ketamine abusers with KIUT (Ke et al. 2014). The difference in results may be due to the small sample size acquired in each study. Thus, future studies involving a larger sample size are warranted.

Cell apoptosis

Apoptosis of bladder tissue is another possible mechanism of KIUT. Increased apoptosis is observed in the bladder tissue of patients with interstitial cystitis/painful bladder syndrome (IC/PBS), overactive bladder of rats, and CP-induced cystitis (Jezernik et al. 2003; Lee et al. 2011; Shie et al. 2012). Similarly, there is a higher number of apoptotic cells in the bladder tissue of chronic ketamine abusers with KIUT (Lee et al. 2013). In addition, Song et al. (2016) reported that an overexpression of apoptotic factor B cell leukemia/lymphoma-2-associated protein (BAX) in the bladders of rats with KIUT. Apoptotic cells in the bladder may undergo secondary necrosis, a process where the cell membrane is permeable to macromolecules that eventually leads to inflammatory responses (Jhang et al. 2015). However, the causal link between cell apoptosis and KIUT-associated bladder inflammation remains undetermined. Further investigations on this relationship are required.

Microvascular damage

In a human KIUT bladder biopsy, the tortuous shape of microvessels and a thicker basement membrane are seen in the endothelium (Lin et al. 2016). The NMDARs are also found on endothelial cells in the bladder; thus, it has been speculated that the antagonism of these receptors by ketamine results in vessel impairment and chronic inflammation (Lin et al. 2016). Microvascular injury in the bladder may cause local ischemia as well, leading to dysuria and pelvic pain (Lin et al. 2016). To date, there is limited data on this possible mechanism of KIUT. More studies are needed to illustrate the importance of microvascular damage in the pathogenesis of KIUT.

Overexpression of carcinogenic genes

Currently, no evidence suggests the development of bladder cancer in chronic ketamine abusers with KIUT, although there are particular features in KIUT that are associated with urothelial carcinoma (Jhang et al. 2015). Urothelial atypia has been found in some chronic ketamine abusers with KIUT, where the enlargement and loss of polarity in urothelial cells are observed and resemble carcinoma in situ (Oxley et al. 2009). Furthermore, moderate to high immunoreactivity of tumor suppressor p53 and cell proliferation marker Ki-67 is found in bladders affected by KIUT, which indicates the presence of carcinoma in situ (Lopez-Beltran et al. 2013; Yin et al. 2006).

Gu et al. (2013) has reported a higher expression of phosphorylated transgelin bladder tissue in animals with KIUT. Transgelin, an actin-binding protein that regulates the actin cytoskeleton, is usually present in smooth muscle and some epithelial tissue (Assinder et al. 2009; Yin et al. 2019). Transgelin might also act as a tumor suppressor, where its loss of expression is seen in prostate, breast, and colon cancers (Assinder et al. 2009). It has been speculated that phosphorylation of transgelin would inactivate the actin-binding process and possibly the tumor-suppressing function of the protein, which could lead to the development of cancer in the organ (Leung et al. 2011).

Lastly, the expression of intercellular junction proteins (E-cadherin) is reduced in bladders affected by KIUT, which may lead to urothelial barrier damage and subsequent inflammatory responses (Wang et al. 2017). Previous studies have observed that the low expression of E-cadherin is correlated with cancer progression (Popov et al. 2000). Carcinogenic factors could thus be a downstream response to persistent inflammation in KIUT of the bladder. Long-term follow-up in chronic ketamine abusers with KIUT will be necessary to explore the causal relationship between KIUT and urothelial carcinoma.

Discussion

Herein, we identified multiple mechanisms that may be involved in the pathophysiology of KIUT, such as urothelial barrier disruption, inflammation in the bladder, ketamine direct toxicity, nerve hyperplasia and hypersensitivity, cell apoptosis, microvascular damage, and overexpression of carcinogenic genes. The foregoing constellation of possible pathophysiological mechanisms that may contribute to KIUT indicates that the actual pathophysiology of KIUT is complex and may result from a combination of several pathways.

The critical pathological change in KIUT is persistent bladder inflammation. It is believed that ketamine in the urine leads to elevated neurotrophin levels and subsequently neurogenic inflammation, induces IgE-mediated inflammation, and stimulates the NOS-COX-prostaglandin pathway (Castellani et al. 2020; Jhang et al. 2015). Chronic inflammation in the bladder could result in collagen deposition and fibrosis, which may cause severe bladder pain and increased urinary frequency. Chronic ketamine abuse could also exert direct toxicity to the bladder, damage the urothelium barrier function, and induce cell apoptosis. Furthermore, the overexpression of carcinogenic genes may be a downstream response to KIUT bladder inflammation.

Nevertheless, there is a limitation to the generalizability of KIUT to the urological symptoms observed in IV ketamine and IN esketamine trials. Chronic ketamine abusers often use multiple substances besides ketamine such as amphetamine, cocaine, and alcohol (Winstock et al. 2012). Thus, it is unclear how much of the urological symptoms can be attributed to ketamine purely.

In recent years, IV ketamine has shown acute antidepressant effects in TRD when administered in sub-anesthetic, repeat doses (0.5–1.0 mg/kg every 1–4 weeks) (aan het Rot et al. 2010; Rodrigues et al. 2020; Singh et al. 2016). It appears to be well-tolerated and effective in the short term (< 6 months). However, the safety profile of long-term IV ketamine treatment (≥ 6 months) in persons with TRD are currently unknown. To date, there is no evidence suggesting ketamine treatment in mood disorders is associated with urological toxicity. For IN esketamine, two clinical studies have reported a low occurrence (< 10%) of urological complications at antidepressant doses (28–84 mg) (Daly et al. 2019; Wajs et al. 2020). Nonetheless, extant data on long-term safety profile (≥ 6 months) of IN esketamine are also limited. To ensure they are feasible, long-term treatment options, more research is needed to examine the safety of long-term IV ketamine and IN esketamine administration (≥ 6 months). Additionally, a more comprehensive understanding of KIUT mechanisms would further inform safety measures in clinical trials and clinical interventions with IV ketamine/IN esketamine and TRD. Therefore, further investigations are required to address these issues. In the interim, the risk of KIUT should be

discussed as part of informed consent for long-term IV ketamine treatment (≥ 6 months), along with routine monitoring of urological signs and symptoms by ketamine providers (Sanacora et al. 2017).

Conclusion

Prior research suggests that the pathogenesis of KIUT is comprised of complex interactions between several physiological pathways. One key pathological change in KIUT is bladder inflammation, which could be the result of neurogenic inflammation, IgE-mediated inflammation, and stimulation of the NOS-COX-prostaglandin pathway. Ketamine could also inflict damage to the urothelium directly and enhance cell apoptosis. Notwithstanding the observations in persons using high-frequency ketamine recreationally, there is no evidence that ketamine or esketamine treatment in mood disorders is associated with KIUT. Despite the absence of KIUT in persons with mood disorders receiving ketamine/esketamine treatment, clinicians are encouraged to inform patients of the potential risks and should specifically probe patients for symptoms and signs that are suggestive of KIUT.

Compliance with ethical standards

Conflict of interest Dr. Roger McIntyre has received research grant support from CIHR/GACD/Chinese National Natural Research Foundation; speaker/consultation fees from Lundbeck, Janssen, Purdue, Pfizer, Otsuka, Allergan, Takeda, Neurocrine, Sunovion, Minerva, Intracellular, Abbvie, and Eisai. Dr. Roger McIntyre is a shareholder and CEO of Champignon.

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